CORRECTED VERSION

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

ASTRAZENECA
Global Intellectual Property,
Patents.
P.O. Box 272
Mereside
Alderley Park
Cheshire SK10 4TG
ROYAUME-UNI

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year)
29 November 2000 (29.11.00)

Applicant's or agent's file reference
PHM.70538/WO

IMPORTANT NOTIFICATION

International application No.
PCT/GB00/01875

International filing date (day/month/year)
16 May 2000 (16.05.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
ASTRAZENECA AB
S-151 85 Södertälje
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [X] the nationality [X] the residence

Name and Address
ASTRAZENECA AB
S-151 85 Södertälje
Sweden

State of Nationality: SE
State of Residence: SE
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[X] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
R. Chrem

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 23 January 2001 (23.01.01)	
International application No. PCT/GB00/01875	**Applicant's or agent's file reference** PHM.70538/WO
International filing date (day/month/year) 16 May 2000 (16.05.00)	**Priority date** (day/month/year) 19 May 1999 (19.05.99)
Applicant REINSTEIN, Michael, J. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

11 December 2000 (11.12.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Juan Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

14

PATENT COOPERATION TREATY

REC'D 12 SEP 2001

WIPO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PHM.70538/WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/01875	16/05/2000	19/05/1999
International Patent Classification (IPC) or national classification and IPC A61K31/00		
Applicant ASTRAZENECA AB		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11/12/2000	10.09.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Brück, M Telephone No. +49 89 2399 8735

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/01875

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-7 as originally filed

Claims, No.:

1-12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-12.

because:

☒ the said international application, or the said claims Nos. 1-12 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5-10
	No:	Claims	1-4,11,12
Inventive step (IS)	Yes:	Claims	5-10
	No:	Claims	1-4,11,12
Industrial applicability (IA)	Yes:	Claims	*

No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Section III

1. Claims 1-10 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2. Cf. Section VIII for the conditions under which the following opinion is valid.

Section V

1. Subject matter

The independent claims relate to a method (claim 1)/ first medical use (claim 11)/second and further medical use (claim 12) of treating the weight (cf. section VIII, 1) and to a method of inducing weight loss (claim 9) with quetiapine.

2. Prior art

D1: WO 98 04289 A (BLACKBURN THOMAS PAUL ;SMITHKLINE BEECHAM PLC (GB)) 5 February 1998 (1998-02-05), describes D2 antagonists such as quetiapine for the treatment of disorders in eating behaviours (pages 2 and 3).

D2: WO 97 32037 A (SMITHKLINE BEECHAM PLC ;KERWIN ROBERT (GB); COLLIER DAVID (GB); RO) 4 September 1997 (1997-09-04), describes a method for assessing the responsiveness of individuls to modulators of the 5-HT2 receptors such as clozapine and olanzapine (pages 1 and 2).

D3: EP-A-0 830 864 (LILLY CO ELI) 25 March 1998 (1998-03-25) describes compositions comprising two antipsychotics such as quetiapine and fluoxetine (pages 2 and 3) and its lack of weight gain (page 12).

D4: WO 00 54764 A (CHILDRENS HOSP RES FOUNDATION) 21 September 2000 (2000-09-21), describes quetiapine as a new atypical antipsychotic with side effects such as weight gain.

3. Novelty and Inventive step

a. Claims 1-4, 11, and 12 are not novel vis-à-vis D1 (cf. item 2).
Claim 11 is not novel vis-à-vis D3 (cf. item 2).
Claim 11 is not novel vis-à-vis D4 (cf. item 2).

b. Claims 5-10 are novel and inventive because the specific induction for weight loss by quetiapine alone or in combination with another psychotic agent has not been disclosed or suggested in the prior art.

4. Industrial applicability

For the assessment of the present claims 1-10 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims.
The EPO does not, for example, recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section VI

1. The following document WO 00/54764 (priority: 18.03.2000, filing: 17.03.2000, publication: 21.09.2000), discloses the treatment of Bulimia Nevosa or Bulimia-Type Eating Disorder with compounds such as clozaine olanzapine, quetiapine and may, therefore, be considered to be a relevant earlier application by certain authorities (see states designated in respect of this earlier application).
Thus, it may be helpful to note that this document might be relevant for lack of novelty of claims 1-6, 10 and 11.

Section VIII

1. The term "treating weight" is not clearly defined and renders, therefore, claims 1-8, 11, and 12 unclear contrary to Article 6 PCT.

   The above opinion will only be valid on condition that this objection has been overcome and that the term "treating weight" has been clarified in terms equivalent to "by inducing weight loss" as described in claim 9 and the specification.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 November 2000 (30.11.2000)

PCT

(10) International Publication Number
WO 00/71106 A3

(51) International Patent Classification[7]: A61K 31/551, 31/554, A61P 3/04, 25/18

(21) International Application Number: PCT/GB00/01875

(22) International Filing Date: 16 May 2000 (16.05.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

9911499.3	19 May 1999 (19.05.1999)	GB
0002762.3	8 February 2000 (08.02.2000)	GB

(71) Applicant *(for all designated States except US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **REINSTEIN, Michael, J.** [US/US]; Forest Hospital/Rush Pres. Hospital, 4735 North Kenmore Street, Chicago, IL 60640 (US). **JONES, Andrew, Martin** [GB/GB]; Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(74) Agent: **ASTRAZENECA**; Global Intellectual Property, Patents., P.O. Box 272, Mereside, Alderley Park, Cheshire SK10 4TG (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
10 May 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/71106 A3

(54) Title: METHOD OF TREATING WEIGHT GAIN

(57) Abstract: A method of treating weight in patients, in particular those suffering from psychoses, by administering the antipsychotic agent quetiapine.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB00/01875

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/551 A61K31/554 A61P3/04 A61P25/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, MEDLINE, CHEM ABS Data, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 04289 A (BLACKBURN THOMAS PAUL ;SMITHKLINE BEECHAM PLC (GB)) 5 February 1998 (1998-02-05) abstract page 1, line 16 - line 20 page 2, line 11 - line 19 page 3, line 5 - line 20 ---	1,11,12
X	WO 97 32037 A (SMITHKLINE BEECHAM PLC ;KERWIN ROBERT (GB); COLLIER DAVID (GB); RO) 4 September 1997 (1997-09-04) page 1, line 3 - line 5 page 1, line 27 - line 31 page 2, line 3 - line 5 page 3, line 16 - line 34 ---	1,11,12

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 June 2001	04/07/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cielen, E

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 830 864 A (LILLY CO ELI) 25 March 1998 (1998-03-25) page 2, line 20 - line 21 page 2, line 50 - line 53 page 3, line 40 - line 58 page 11, line 37 - line 48 page 12, line 39 - line 48 claims 1,2,8,9 ---	1,11,12
X	MISRA L K ET AL: "Quetiapine: a new atypical antipsychotic." SOUTH DAKOTA JOURNAL OF MEDICINE, (1998 JUN) 51 (6) 189-93. REF: 13 , XP000901163 abstract page 192, column 1, paragraph 2 - paragraph 3 ---	1,11
A	LEYSEN J.E. ET AL: "Receptor interactions of new antipsychotics: Relation to pharmacodynamic and clinical effects." INTERNATIONAL JOURNAL OF PSYCHIATRY IN CLINICAL PRACTICE, (1998) 2/SUPPL. 1 (S3-S17). , XP001009585 abstract figures 2,3 page S8, column 1, paragraph 3 -column 2, paragraph 1 page S10, column 2, paragraph 2 page S11, column 1, paragraph 5 page S12, column 1, paragraph 3 table 3 page S14, column 1, paragraph 3 -column 2, paragraph 3 ---	
A	ANONYMOUS: "Adverse effects of the atypical antipsychotics. Collaborative Working Group on Clinical Trial Evaluations." JOURNAL OF CLINICAL PSYCHIATRY, (1998) 59 SUPPL 12 17-22. REF: 57 , XP001009550 table 1 page 19, column 1, paragraph 4 -column 2, paragraph 2 page 21, column 1, paragraph 3 --- -/--	

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/01875

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	ROBERTSON J B JR ET AL: "Successful use of high dose quetiapine in a patient with a psychiatric disorder resistant to olanzapine." EUROPEAN NEUROPSYCHOPHARMACOLOGY, vol. 10, no. Supplement 3, September 2000 (2000-09), pages S319-S320, XP001010838 13th Congress of the European College of Neuropsychopharmacology;Munich, Germany; September 09-13, 2000 ISSN: 0924-977X the whole document	1,2,4,5, 7-12
P,X	NASR S J: "Resolution of rapid weight gain on olanzapine after substitution with quetiapine." EUROPEAN NEUROPSYCHOPHARMACOLOGY, vol. 10, no. Supplement 3, September 2000 (2000-09), page S319 XP001009548 13th Congress of the European College of Neuropsychopharmacology;Munich, Germany; September 09-13, 2000 ISSN: 0924-977X the whole document	1,2,4,5, 7-12
P,X	REINSTEIN MICHAEL J ET AL: "Effect of clozapine-quetiapine combination therapy on weight and glycaemic control: Preliminary findings." CLINICAL DRUG INVESTIGATION, vol. 18, no. 2, August 1999 (1999-08), pages 99-104, XP001009552 ISSN: 1173-2563 abstract page 100, column 2, paragraph 2 page 101, column 2, paragraph 4 page 102, column 1, paragraph 4 page 102, column 2, paragraph 4 - paragraph 5 page 103, column 1, paragraph 3 -column 2, paragraph 1	1-7,9-12
E	WO 00 54764 A (CHILDRENS HOSP RES FOUNDATION) 21 September 2000 (2000-09-21) abstract page 1, line 3 - line 9 page 4, line 15 - line 27 page 5, line 24 -page 6, line 18 page 7, line 1 - line 14 claims 1,2	1,2,11, 12

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/01875

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9804289 A	05-02-1998	AU 725817 B	19-10-2000
		AU 4297297 A	20-02-1998
		BR 9710568 A	17-08-1999
		CN 1230894 A	06-10-1999
		CZ 9900237 A	16-06-1999
		EP 0936924 A	25-08-1999
		HU 9903619 A	28-10-2000
		JP 2000516924 T	19-12-2000
		NO 990322 A	24-03-1999
		PL 331426 A	19-07-1999
		TR 9900140 T	22-03-1999
		ZA 9706593 A	25-01-1999
WO 9732037 A	04-09-1997	AU 1878997 A	16-09-1997
		JP 2000506009 T	23-05-2000
EP 0830864 A	25-03-1998	AU 719033 B	04-05-2000
		AU 4411297 A	14-04-1998
		BR 9711530 A	24-08-1999
		CN 1230886 A	06-10-1999
		CZ 9900987 A	15-12-1999
		HU 9903905 A	28-10-2000
		JP 2001503031 T	06-03-2001
		NO 991381 A	22-03-1999
		PL 332481 A	13-09-1999
		WO 9811897 A	26-03-1998
		US 6147072 A	14-11-2000
		ZA 9707967 A	04-03-1999
WO 0054764 A	21-09-2000	AU 3757500 A	04-10-2000

PCT

D INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C12Q 1/68, A01K 67/027, C12N 5/10

A1

(11) International Publication Number: WO 97/32037

(43) International Publication Date: 4 September 1997 (04.09.97)

(21) International Application Number: PCT/EP97/00993

(22) International Filing Date: 26 February 1997 (26.02.97)

(30) Priority Data:
9604465.6 1 March 1996 (01.03.96) GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: KERWIN, Robert [GB/GB]; Institute of Psychiatry, The Maudsley Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF (GB). COLLIER, David [GB/GB]; Institute of Psychiatry, The Maudsley Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF (GB). ROBERTS, Gareth, Wyn [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: GARRETT, Michael; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: ASSESSMENT OF THE RESPONSIVENESS OF INDIVIDUALS TO MODULATORS OF THE 5-HT$_2$ RECEPTORS, ESPECIALLY THE 5-HT$_{2A}$ RECEPTOR

(57) Abstract

A method for use in assessing in a subject suffering from a condition which may be treated with a 5-HT$_2$ modulator the likelihood whether said subject will be responsive or non-responsive to treatment with a 5-HT$_2$ modulator, the method comprising detecting the presence or absence of DNA encoding the Tyr452 and/or His452 alleles of the 5-HT$_{2A}$ gene in a biological sample obtained from said subject.

FOR THE PURPOSES OF INFORMATION ONLY

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ASSESSMENT OF THE RESPONSIVENESS OF INDIVIDUALS TO MODULATORS OF THE 5-HT_2 RECEPTORS, ESPECIALLY THE 5-HT_{2A} RECEPTOR

The present invention relates to methods of assessing the responsiveness of individuals to therapeutic agents which interact with 5-HT_2 receptors, in particular the 5-HT_{2A} receptor, and especially to neuroleptic agents such as clozapine.

Schizophrenia is a devastating psychiatric disease for which there is currently no cure, although advances are now being made in understanding its causes and controlling its symptoms. In general the age of onset is in late adolescence and it is a lifelong illness with a very poor prognosis. Subjects suffering from schizophrenia may exhibit positive symptoms, for example delusions and hallucinations, and /or negative symptoms such as withdrawal, isolation and demotivation leading ultimately to social decline and suicide. There are around 600,000 schizophrenics at any one time in the UK and their care has been reported to cost approximately 1.6% of the total healthcare budget. Most of these costs are non-drug, community and hospital costs. Therefore better targetting of effective drug treatments has the potential for considerable economic savings. (British Journal of Psychiatry, (1994) 165 (suppl.25), 18-21).

Since the 1950's antipsychotic drugs (neuroleptics) have been available and are used with varying degrees of success to treat the positive symptoms of schizophrenia. However, the majority of these agents ("typical" neuroleptics) have little effect on the negative symptoms of schizophrenia and furthermore have a number of side effects, the most distressing of which are movement disorders known as extrapyramidal side effects (eps). Examples of typical neuroleptics include haloperidol and sulpiride. Over 90% of patients in the UK are treated with such traditional antipsychotics but some 30% of patients fail to respond. The therapeutic effect of typical antipsychotic agents is believed to be exerted principally via blockade of dopamine D_2 receptors; however this mechanism is also thought to be responsible for the extrapyramidal side effects.

More recently second generation antipsychotic agents, so-called "atypical" neuroleptics, having enhanced efficacy and fewer side effects have been developed. These compounds appear to have a lower affinity for D_2 receptors than do the typical neuroleptics but they also interact with other receptors, eg the dopamine D_4 receptor and serotonin receptors, notably the serotonin 5-HT_{2A} and 5-HT_{2C} receptors. Atypical neuroleptics provide advantages in that they improve both the positive and negative symptoms of schizophrenia and cause virtually no eps. An example of this type of drug is clozapine. However, its use has been severely limited by controversy over its propensity to produce neutropenia and its expense; hence it is reserved for the treatment of schizophrenia in subjects who do not respond to other neuroleptics. In addition there remains a proportion of patients who are resistant to treatment even with clozapine. A

test, therefore, that helps to predict those patients most likely to benefit would be a valuable clinical decision making tool.

Further examples of "atypical" neuroleptics include risperidone, olanzapine, seroquel, sertindole and ziprasidone; all are antagonists at both dopamine D_2 and 5-HT_{2A} receptors.

Once schizophrenia has been diagnosed it is clearly desirable to select and administer the most appropriate therapy as quickly as possible. At present treatment with neuroleptics is largely a matter of trial and error, as there is no way of determining in advance whether a patient is likely to be responsive to drug treatment. Hence a patient may undergo several courses of treatment with various antipsychotic agents before non-responsiveness is established. In view of the side effects of these drugs it would be highly beneficial to avoid giving them to patients who may never respond to the treatment (non-responders); this is particularly important in the case of clozapine, in view of its known toxicity profile. Furthermore, it is generally found that the long-term outcome of the disease is improved if a patient is given the most effective drug therapy at the outset, rather than after one or more inappropriate drugs. Therefore a means of targetting those patients more likely to respond to drug therapy would be advantageous.

Recently it has been found that the human serotonin receptor gene encoding for the 5-HT_{2A} receptor exhibits a coding mutation His452Tyr, comprising two alleles, His452 and Tyr452, which have been found to occur in the general population with a frequency of 91% and 9% respectively, with an observed heterozygosity of 16.4%. These alleles give rise to three distinct genotypes, His452/His452; His452/Tyr452 and Tyr452/Tyr452. (Lancet, Vol 346, No. 8979, p908-909, 30 Sept 95). However, no association between these variants and response to clozapine amongst a group of schizophrenic patients has been reported.

It has now surprisingly been found that in a population of diagnosed schizophrenic patients treated with clozapine the distribution of alleles His452 and Tyr452 between patients who respond to treatment with clozapine (hereinafter "responders") and those who fail to respond to such treatment (hereinafter "non-responders") is significantly different from that in the general population. In particular the proportion of non-responders found to be homozygous for the Tyr452 allele was higher than would be expected from the frequency of this genotype in the general population. However, amongst the patients found to be homozygous for the His452 allele or those who were heterozygous, there was no significant difference between the proportions of responders and non-responders. Thus there is a correlation between homozygosity for the Tyr452 allele and failure to respond to treatment with clozapine.

This allelic variation can therefore be utilised to predict which patients are least likely to repond to treatment with clozapine.

The present invention therefore provides an objective method for use in assessing in a subject the likelihood whether said subject will be non-responsive to treatment with clozapine, the method comprising detecting the presence of DNA encoding the Tyr452 allele and/or the His452 allele of the 5-HT_{2A} gene in said subject.

The method of the present invention may also be used more generally in assessing whether a subject is likely to be responsive or non-responsive to a therapeutic agent which acts at 5-HT_2 receptors, in particular the 5-HT_{2A} receptor. Compounds acting at these receptors will hereinafter be referred to as 5-HT_2 and 5-HT_{2A} modulators. Such compounds include both typical and atypical neuroleptic agents

The present invention therefore provides a method for use in assessing whether a subject will be responsive or non-responsive to treatment with a 5-HT_2 modulator, the method comprising testing for and detecting the presence or absence of DNA comprising the Tyr452 allele and/or the His452 allele of the 5-HT_{2A} gene in said subject.

Preferably, the method is used in assessment of the likelihood of response or non-response to a 5-HT_{2A} modulator. 5-HT_2 and 5-HT_{2A} modulators include agonists and antagonists at these receptors. Such compounds may exert a variety of therapeutic effects. Thus for example 5-HT_{2A} antagonists may be of potential use in the treatment of CNS disorders such as schizophrenia, depression, manic-depressive illness, obsessive compulsive disorders, panic disorders, post-traumatic stress disorders, generalised anxiety disorders, feeding disorders such as anorexia and bulimia, anhedonia, sexual dysfunction, premenstrual syndrome, migraine, epilepsy, Alzheimers disease, sleep disorders, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, drug eg cocaine craving, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus.

In a particularly preferred embodiment the invention provides a method for use in assessing in a subject diagnosed as suffering from schizophrenia the likelihood that said subject will be non-responsive or responsive to a neuroleptic agent, the method comprising testing for and detecting the presence or absence of DNA comprising the Tyr452 allele and/or the His452 allele of the 5-HT_{2A} gene in said subject. The neuroleptic agent is preferably a modulator of a 5-HT_2 receptor, especially a 5-HT_{2A} receptor modulator. Advantageously the neuroleptic agent is an 'atypical' neuroleptic agent such as, clozapine, risperidone, olanzapine, seroquel, sertindole or ziprasidone. Most preferably the neuroleptic agent is clozapine. Preferably the method is used to assess likelihood of non-response. In the case of clozapine, the presence of 5-HT_{2A} Tyr452 alone, ie where the subject is homozygous for the Tyr452 allele, indicates that the

subject will be less likely to respond (ie will have a lower probability of response) to treatment with this agent. In this context 'lower probability' means that the likelihood of response is lower than the 'normal' response rate, ie the response rate observed for a random group of schizophrenic patients.

It will of course be understood by practitioners skilled in the treatment of conditions such as those listed above, in particular schizophrenia, that the method of the present invention does not give a precise or absolute identification of responders and non-responders but rather indicates the degree or likelihood of responsiveness and so can be used to aid and guide the clinical judgement of the physician.

Those skilled in the treatment of schizophrenia will also appreciate that the terms "responders" and "non-responders" as used herein are terms well known in the art. In the clinic the degree of responsiveness to a neuroleptic agent such as clozapine is generally assessed according to well-established rating scales, such as the Global Assessment Scale (GAS) or the Brief Psychiatric Rating Scale (BPRS).

In a further embodiment the present invention provides a method for assessing whether a subject suffering from a condition which may be treated with a 5-HT_2 modulator will be responsive or non-responsive to treatment with a 5-HT_2 modulator, said method comprising the steps of:

(i) testing for the presence or absence of DNA encoding the Tyr452 and/or His452 allele of the 5-HT_{2A} gene in a sample containing DNA obtained from said subject, and

(ii) comparing the result with a pre-determined correlation between the distribution of Tyr452 and/or His452 alleles and the response to said 5-HT_2 modulator obtained for a population of subjects suffering from said condition.

The pre-determined correlation utilised in step (ii) may itself be obtained by the following series of steps:

selecting a population or cohort of subjects diagnosed as suffering from a specified condition;

treating said cohort with a specified 5-HT_2 (eg 5-HT_{2A}) modulator;

monitoring the outcome of said treatment and identifying responders and non-responders to the said treatment,

taking from said cohort biological samples containing DNA and testing this for the presence or absence of the Tyr452 and/or His452 alleles of the 5-HT_{2A} gene;

analysing the distribution of alleles as between responders and non-responders;

making a comparison with the distribution of alleles in a control group of subjects, not suffering from said condition;

performing a statistical analysis to determine if there is a statistically significant association between presence or absence of the Tyr452 and/or His452 alleles and response to treatment.

The present invention thus also provides a method for assessing whether a subject suffering from a condition which may be treated with a 5-HT_2 (eg a 5-HT_{2A}) modulator will be responsive or non-responsive to treatment with a specified 5-HT_2 modulator, said method comprising the steps of:

(i) correlating the distribution of 5-HT_{2A} Tyr452 and 5-HT_{2A} His452 alleles in a population of subjects suffering from a specified condition requiring treament with a 5-HT_2 modulator with observed clinical response to said modulator;

(ii) testing for the presence or absence of DNA encoding the Tyr452 and/or His452 allele of the 5-HT_{2A} gene in a sample containing DNA obtained from said subject, and

(iii) comparing the result obtained in (ii) with the correlation between the distribution of Tyr452 and His452 alleles and the response to said 5-HT_2 modulator obtained in (i).

Step (i) will itself comprise taking from the subjects biological samples containing DNA and testing this for the presence or absence of the alleles. It will be appreciated that where the correlation in (i) is known , eg as in the case of clozapine, the process comprises only steps (ii) and (iii).

In a yet further aspect the invention provides a method for generating a model to assess whether a subject is likely to be responsive or non-responsive to treatment with a 5HT_2 (eg a 5-HT_{2A}) modulator which method comprises:

(i) treating a cohort of patients diagnosed as suffering from a specified condition (eg schizophrenia) which may be treated with a 5HT_2 modulator (eg clozapine) with said 5HT_2 modulator;

(ii) assessing the outcome of treatment so as to define responders and non-responders according to pre-determined criteria;

(iii) obtaining DNA samples from the cohort of patients in (i);

(iv) obtaining DNA samples from a control group of subjects diagnosed as not suffering from said condition;

(v) analysing the samples obtained in (iii) and (iv) to identify whether they encode the Tyr452 allele or the His452 allele of the 5-HT_{2A} gene or both alleles;

(vi) calculating the distribution of Tyr452 and His452 alleles in the samples from (iii) for responders and non-responders;

(vii) calculating the distribution of Tyr452 and His452 alleles in the samples from (iv);

(viii) comparing the distributions obtained in (vi) and (vii);

(ix) comparing the distribution obtained in (vi) as between responders and non-responders

(x) performing statistical analysis on the results from (viii) and (ix) to generate a model for asssessing the probability of response to treatment with said $5HT_2$ modulator, based on whether a subject possesses the Tyr452 and/or His452 allele.

The invention also provides a method for assessing whether a subject suffering from a condition which may be treated with a 5-HT_2 (eg a $5HT_{2C}$) modulator will be responsive or non-responsive to treatment with a specified 5-HT_2 modulator, which comprises comparing said subject's genotype with the model described above.

It will be appreciated that in any of the above methods, one or more of the steps may be effected by a computer-controlled system. Thus, for example, once the biological samples have been obtained, genotyping may be carried out by a computer-controlled robotic system. A computer-controlled system may also be configured to make the comparison between the subject to be assessed and a pre-determined correlation or model. A computer controlled system may also be configured to give either a positive or negative readout depending on the outcome of the comparison. The present invention therefore extends to such computer-controlled or computer-implemented methods.

The step of testing for and detecting the presence of DNA encoding Tyr452 and/or His452 alleles may be carried out either directly or indirectly by any suitable means, such as by techniques well known in the art, and is preferably carried out *ex vivo* All generally involve the step of collecting a sample of biological material containing DNA from the subject, and then detecting which alleles the subject possesses from that sample. For example, the detecting step may be carried out by collecting a biological sample containing DNA from the subject, and then determining the presence of DNA comprising a Tyr452 and/or His452 allele in the biological sample. Any biological sample which contains the DNA of that subject may be employed, including tissue samples and blood samples, with blood cells being a particularly convenient source. Determining the presence of DNA comprising a Tyr452 and/or His452 allele may be carried out with an oligonucleotide probe labelled with a suitable detectable group; by means of an amplification reaction such as a polymerase chain reaction or ligase chain reaction (the product of which amplification reaction may then be detected with a labelled oligonucleotide probe) or by means of restriction nuclease digestion and electrophoretic separation to detect restriction fragment length polymorphism (RLFP). Further, the detecting step may include the step of detecting whether the subject is

heterozygous or homozygous for the gene encoding a Tyr452 or His452 allele. Numerous different oligonucleotide probe assay formats are known which may be employed to carry out the present invention.

It will readily be appreciated that the detecting steps may be carried out directly or indirectly. Thus, for example, any of the techniques described above may be used to detect either the Tyr452 allele or the His452 allele. If only the Tyr452 allele is detected in the subject, then it is determined that the subject is homozygous for allele Tyr452; but if allele His452 is detected in the subject, either alone or in addition to allele Tyr452 then it is determined that the subject is either homozygous for His452 or heterozygous.

The present invention has utility in enabling improvements in the clinical management of patients suffering from schizophrenia. By identifying in advance of treatment those who are not likely to respond to neuroleptics such as clozapine, it will be possible to avoid unecessary and non-beneficial adminstration of such drugs together with the associated side effects and costs and instead to select a more appropriate form of therapy. Thus the invention provides direct benefits to the patient in terms of indicating the most appropriate therapy as early as possible in the treatment process and is of wider benefit in terms of health economics.

In a further embodiment therefore the present invention provides a method of treating a condition which requires treatment with a 5-HT_2 modulator, said method comprising:

(i) testing for DNA comprising allele Tyr452 and/or His452 in a sample of biological material containing DNA obtained from a subject suffering from said condition, and

(ii) if DNA comprising the His452 allele, either alone or in the presence of the Tyr452 allele, is present in the sample, treating said subject with a 5-HT_2 modulator.

Preferably the condition is schizophrenia. The 5-HT_2 modulator is preferably a neuroleptic agent, such as clozapine.

In addition the invention has utility in enabling effective and efficient design of clinical trials with 5-HT_2 modulators such as neuroleptic agents. Thus in comparative trials with two or more neuroleptics, patients who are not likely to respond to either or any of the agents can be excluded.

It is believed that the presence of the Tyr452 allele is also associated with a greater probability or risk of developing schizophrenia. Thus the presence of this allele can be used prognostically in assessing the likelihood that a given subject will develop schizophrenia. The present invention therefore also provides a method for use in assessing whether a subject is likely to develop schizophrenia, the method comprising

testing for and detecting the presence or absence of DNA comprising the Tyr452 allele and/or the His452 allele of the 5-HT_{2A} gene in said subject.

In a further embodiment the invention also provides an assay suitable for use in the methods of the present invention said assay comprising means for determining the presence of DNA encoding allele Tyr452 and/or allele His452 in a biological sample.

The present invention also provides a kit suitable for use in the methods of the present inventions, said kit comprising

(a) means for testing for the presence or absence of DNA encoding allele Tyr452 and/or His452 in a sample of human DNA;

(b) reagents for use in the detection process.

The means for testing preferably comprises a labelled probe or a restriction enzyme. The reagents may comprise for example diluents, wash solutions and control solutions.

In a further embodiment the present invention provides a cell line which expresses DNA encoding the human 5-HT_{2A} Tyr452 and/or His452 alleles. Preferably the cell line expresses DNA encoding the human 5-HT_{2A} Tyr452 allele. Such cell lines can be obtained using known recombinant techniques and methodology.

In a yet further embodiment the present invention also provides a transgenic animal, in particular a transgenic mammal such as a mouse, which expresses the human 5-HT_{2A} gene containing the Tyr452 allele. Such a transgenic animal may be used to screen for and identify novel antipsychotic agents that are likely to be effective in patients who do not respond to currently available neuroleptics such as clozapine. Transgenic animals homozygous for the Tyr452 allelic variant of the h5HT_{2A} gene may be obtained using procedures which are standard in the field of genetic engineering.

EXAMPLE

Method

Genotyping for His452Tyr polymorphism was carried out using blood samples obtained from individuals diagnosed as suffering from schizophrenia (DSM III) and undergoing treatment with clozapine. The individuals were also separately assessed for responsiveness to clozapine treatment: non-response is defined as a drop of <20 points on GAS or <20% on BPRS after six weeks treatment. The results were correlated as shown in the table below.

Detection of His452Tyr polymorphism

Methods described by Erdmann et al (1996, Human Genetics, ref: (1996) 97(5) p614-619) with modification of PCR conditions as follows:

Standard PCR carried out in 25µl volume containing 100ng genomic DNA, 10pmol each primer, 50mM KCl, 10nM Tris-HCl, 2.0mM $MgCl_2$, 0.01% gelatin, 200µM dNTPs and 1 U Taq DNA polymerase.

Primers:

5'-CAAAGCAAGATGCCAAGACA-3'

5-GGCATACAGATATGATCGTTGG-3'

PCR programme:

95°C for 1', followed by 35 cycles of 95°C for 45", 58°C for 45", 72°C for 45", final elongation step of 72°C for 10'.

Allele detection:

PCR product digested with BbvI (15µl of PCR product, 2µl 1OX RE buffer, 2µl of H_2O, 1µl (10 units) of BbvI) at 37°C for a minimum of 2 hours

digested products run in a 3% Agarose gel for 3 hours at 70v:

PCR product: 248bp

Allele His452: digested in two fragments of 180bp and 68bp

Allele Tyr452: uncut (248 bp).

Results

5-HT2$_a$ Receptor Gene and Clozapine Analysis of His452Tyr Polymorphism

	Responders	Non-responders
His452/His452	87 (88%)	45 (83%)
His452/Tyr452	11 (11%)	6 (11%)
Tyr452/Tyr452	1 (1%)	3 (6%)
No. patients	99	54
Allele		
His452	185 (93%)	96 (89%)
Tyr452	13 (7%)	12 (11%)

Genotypic frequencies: $\chi^2 = 2.84$ $p = 0.24$

Allelic frequencies: $\chi^2 = 1.92$ $p = 0.16$

Claims:

1. A method for use in assessing in a subject suffering from a condition which may be treated with a 5-HT_2 modulator the likelihood whether said subject will be responsive or non-responsive to treatment with a 5-HT_2 modulator the method comprising detecting the presence or absence of DNA encoding the Tyr452 and/or His452 alleles of the 5-HT_{2A} gene in a biological sample obtained from said subject.

2. A method according to Claim 1 wherein the 5-HT_2 modulator acts at the 5-HT_{2A} receptor.

3. A method according to Claim 1 or Claim 2 wherein the 5-HT_2 modulator is an antagonist at said 5-HT_2 receptor.

4. A method according to any of claims 1 to 3 wherein the condition is schizophrenia.

5. A method according to any of claims 1 to 4 wherein the5-HT_2 modulator is a neuroleptic agent.

6. A method as claimed in claim 5 wherein the neuroleptic agent is atypical.

7. A method as claimed in claim 6 wherein the neuroleptic agent is clozapine.

8. A method as claimed in claim 6 wherein the neuroleptic agent is risperdone.

9. A method as claimed in claim 6 wherein the neuroleptic agent is selected from olanzapine, seroquel, sertindole and ziprasidone.

10. A method for assessing whether a subject suffering from a condition which may be treated with a 5-HT_2 modulator will be responsive or non-responsive to treatment with a 5-HT_2 modulator, said method comprising the steps of:

(i) testing for the presence or absence of DNA encoding the Tyr452 and/or His452 alleles of the 5-HT_{2A} gene in a sample containing DNA obtained from said subject, and

(ii) comparing the result with the correlation between the distribution of Tyr452 and His452 alleles and the response to said 5-HT_2 modulator obtained for a population of subjects suffering from said condition.

11. A method according to claim 10, said method comprising the steps of:

(i) correlating the distribution of Tyr452 and His452 alleles in a population of subjects suffering from a specified condition requiring treament with a 5-HT_2 modulator with observed clinical response to said modulator;

(ii) testing for the presence or absence of DNA encoding the Tyr452 and/or His452 allele of the 5-HT_{2A} gene in a sample containing DNA obtained from said subject, and

(iii) comparing the result obtained in (ii) with the correlation between the distribution of Tyr452 and His452 alleles and the response to said 5-HT_2 modulator obtained in (i) for a population of subjects suffering from said condition.

12. A method for generating a model to assess whether a subject is likely to be responsive or non-responsive to treatment with a $5HT_2$ modulator which method comprises:

(i) treating a cohort of patients diagnosed as suffering from a specified condition which may be treated with a $5HT_2$ modulator with said $5HT_2$ modulator;

(ii) assessing the outcome of treatment so as to define responders and non-responders according to pre-determined criteria;

(iii) obtaining DNA samples from the cohort of patients in (i);

(iv) obtaining DNA samples from a control group of subjects diagnosed as not suffering from said condition;

(v) analysing the samples obtained in (iii) and (iv) to identify whether they encode the Tyr452 or His452 allele of the 5-HT_{2A} gene or both alleles;

(vi) calculating the distribution of Tyr452 and His452 alleles in the samples from (iii) for responders and non-responders;

(vii) calculating the distribution of Tyr452 and His452 alleles in the samples from (iv);

(viii) comparing the distributions obtained in (vi) and (vii);

(ix) comparing the distribution obtained in (vi) as between responders and non-responders;

(x) performing statistical analysis on the results from (viii) and (ix) to generate a model for asssessing the probability of response to treatment with said $5HT_2$ modulator, based on whether a subject possesses the Tyr452 and/or His452 allele of the 5-HT_{2A} gene.

13. A method for assessing whether a subject suffering from a condition which may be treated with a 5-HT_2 modulator will be responsive to treatment with a specified 5-HT_2 modulator, which comprises comparing said subject's genotype with a model as claimed in claim 12.

14. A method according to any of claims 10 to 13 wherein at least one step is effected by a computer controlled system.

15. A method according to any of claims 10, 11, 13 or 14 which is configured to detect the Tyr452 allele.

16. A method according to any of claims 1 to 15 wherein detection of the Tyr452 allele is indicative of poor likelihood response to treatment with said 5-HT_2 modulator.

17. A method according to any of claims 10 to 16 wherein the condition is schizophrenia.

18. A method according to any of claims 10 to 17 wherein the 5-HT_2 modulator is a neuroleptic agent.

19. A method for use in assessing whether a subject is likely to develop schizophrenia, the method comprising testing for and detecting the presence or absence of DNA comprising the Tyr452 allele and/or the His452 allele of the 5-HT_{2A} gene in said subject.

20. A cell line which expresses DNA encoding the human 5-HT_{2A} Tyr452 and/or His452 alleles of the 5-HT_{2A} gene.

21. An assay comprising means for determining the presence or absence of DNA comprising Tyr452 and/or His452 alleles in a biological sample.

22. A kit suitable for use in assessing the responsiveness of a subject to a $5HT_2$ modulator, said kit comprising:
(a) means for testing for the presence or absence of DNA encoding Tyr452 and/or His452 alleles in a sample of human DNA;
(b) reagents for use in the detection process.

23. A transgenic mammal which expresses the human 5-HT_{2A} gene comprising the Tyr452 allele.

24. A transgenic mammal which expresses the human 5-HT_{2A} gene comprising the His452 allele.

25. Use of a transgenic mammal according to claim 23 or claim 24 in screening compounds for antipsychotic activity.

INTERNATIONAL SEARCH REPORT

Inten nal Application No
PC[redacted] 97/00993

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12Q1/68 A01K67/027 C12N5/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THE LANCET, vol. 346, September 1995, pages 908-909, XP002034248 NÖTHEN M ET AL: "Genetic variation of 5-HT2A receptor and response to clozapine"	21
A	see page 908, paragraph 3 - page 909, paragraph 4	1-19

A	WO 95 06117 A (SMITHKLINE BEECHAM PLC ;CAREY JANET ELIZABETH (GB); FLANIGAN THOMA) 2 March 1995 see the whole document	1-19, 21-25

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
2 July 1997	14.07.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Osborne, H

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INTERNATIONAL SEARCH REPORT

[redacted] Application No
[redacted]CT/EP 97/00993

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	THE LANCET, vol. 346, July 1995, pages 281-82, XP002034249 ARRANZ M ET AL: "Association between response and allelic variation in 5-HT2a receptor gene" see the whole document ---	1-19,21, 22
T	AMERICAN JOURNAL OF PSYCHIATRY, pages 1092-94, XP002034252 MALHOTRA A ET AL: "Lack of association betweem polymorphism at the 5-HT2A receptor gene and the antipsychotic response to clozapine" see the whole document -----	1-19,21, 22

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

information on patent family members

Inte[illegible]nal Application No
PC[illegible] 97/00993

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9506117 A	02-03-95	EP 0665887 A	09-08-95
		JP 8502902 T	02-04-96

Form PCT/ISA/210 (patent family annex) (July 1992)